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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,135	06/29/2006	Giampiero de Luca	SER-104	1670

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EXAMINER	
SNYDER, STUART	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,135	DE LUCA, GIAMPIERO	
	Examiner	Art Unit	
	STUART W. SNYDER	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/6/2008 has been entered.

2. Claims 14-38 are pending and examined herein. The Examiner erroneously omitted reference to claims 37 and 38 added in Applicants' filing of 7/8/2008.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 14-38 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the Invention: The claims are drawn to a method of treating Severe Acute Respiratory Syndrome (SARS) comprising the

administration of a composition comprising an interferon to an individual having SARS. For the purpose of examination, the term individual refers to animals capable of being infected with SARS-CoV and manifesting clinical symptoms of such an infection.

State Of The Prior Art: The interferons (IFNs) were discovered in 1957 as biological agents interfering with virus replication (Isaacs and Lindenmann (1957)). They are a family of secreted proteins occurring in vertebrates and can be classified as cytokines. The importance of the IFNs in host resistance to viral infections was revealed by injecting mice with antibodies to IFNs which markedly enhanced the susceptibility of the mice to disease caused by infection with various viruses (Gresser, I. (1990). Treatment with IFN proved to be beneficial in the case of numerous human viral diseases including coronaviruses (Higgins, et al. (1983)) and chronic infection with hepatitis B and C viruses (Baron, et al. (1991) This reference is being relied upon specifically for the teachings in the Abstract).

At the time of filing of the instant Application, especially including the filing of priority documents, the etiological agent of the epidemic SARS was just discovered (see, Drosten, et al. 2003 and Holmes, et al., 2003 and references therein, especially No. 6, 8, and 10-12). Treatments for SARS begin in the People's Republic of China (PRC) in January of 2003 and included the following: Ribavirin plus cefoperazone/sulbactam plus or

minus prednisolone, fluoroquiinolone plus azithromycin plus recombinant IFN-alpha plus or minus prednisolone (see, Zhao, et al., 2003) essentially antivirals and antibiotics with relatively broad range of efficacies with and without corticosteroids. Shortly thereafter, Loutfy, et al. (2003) prospectively studied combination of recombinant IFN-alpha and corticosteroids for treatment of humans with SARS and found that the combination was more effective than the use of corticosteroids alone in relieving clinical manifestations of the disease.

In vitro and non-human primate models have suggested that IFNs may be useful in treatment of SARS. Zheng, et al. (2004) demonstrated that type I IFNs protect FRhk-4 cells from viral pathogenesis. Haagmans, et al. (2004) demonstrate PEGylated IFN-alpha protected macaques' pneumocytes from SARS-CoV infection.

Non-patent reviews of sparse clinical data suggest that it is reasonable to study IFN to treat SARS, but that the data are inconclusive with respect to the efficacy. Pyrc, et al. (2007) teaches "treatment with IFN-alpha during the SARS-CoV outbreak showed no benefit" in reference to a report by Zhao, et al (2003). Tai (2007) teaches "IFN is not recommended as standard therapy in SARS" (see Abstract and Interferons section) in reference to the studies of Zhao, et al. and Loutfy, et al. Finally, Stockman, *et al.* conducted a meta-analysis of many experimental SARS-CoV treatment studies and conclude that "Despite an extensive literature

reporting on SARS treatments, it was not possible to determine whether treatments benefited patients during the SARS outbreak." Such studies included three *in vivo* studies using IFN for treatment of SARS in humans and determined that none were conclusive because of "lack of a consistent treatment regimen or suitable control group" and "a variety of treatments given masked the effect of IFN–α alone". Haagmans and Osterhaus (2008) teaches "[PEGylated IFN-alpha and IFN-alphacon-1] could be considered for treatment of SARS should it re-emerge". Thus, the three reports of clinical experience give conflicting results because conclusions with respect to the efficacy of IFN-alpha is confounded by the inclusion of corticosteroids and/or other antivirals prior to or concurrent with the use of IFN in both studies.

Breadth of the Claims: The claims are very broad, encompassing a method for treating SARS comprising administering an IFN. Natural hosts of SARS have been shown to include civets and other species native to China (Guan, et al. 2003) and humans. Laboratory hosts include non-human primates (see, Zheng, et al.) as well as other feline species and ferrets (see, Martina, et al.) and suckling mice (see, Ksiazek, et al.). IFN encompasses many forms of the cytokine including alpha, beta, gamma, lambda, tau, and omega; e.g., types I, II and III interferons.

Working Examples: No working examples are described by Applicants.

Guidance in the Specification: The Specification provides prophetic examples of a proposed clinical trial for the use of interferons in humans using two different dosages of interferon beta. Specific guidance is given for the age group (<18 yo), dosage (1 or 3 million units/m^2/day), duration of treatment (1-4 weeks), and data collected (virus titers of clinical samples as well as clinical observations and other laboratory findings).

Predictability of the Art: As described above, the predictability of the use of IFN in treatment of SARS is controversial. The two clinical studies that included IFN were conducted on extremely sick persons for whom palliative care had been initiated in a clinical setting. Three to four years after these studies, three coronavirus experts advised against IFN in SARS therapy (see, Pyrc, et al., Tai, and Stockman) in part because of the role of IFNs in the pathology of the disease and also because of the lack of suitable controls. On the other hand, another expert suggest that PEG interferon be used should SARS re-emerge into the human population primarily because of lack of other medically approved antivirals being readily available (see, Haagmans and Osterhaus). Thus, the preponderance of opinion amongst experts is against use of IFN in humans.

The art of antiviral therapy in general with IFN is highly unpredictable. For example, treatment of HCV infection is highly dependent on the genotype of the virus; combination therapy with PEGylated interferon and ribavirin is

the treatment of choice resulting in sustained response rates of 40%-80% (up to 50% for patients infected with the most common genotype found in the U.S. [genotype 1] and up to 80% for patients infected with genotypes 2 or 3).

Amount of Experimentation: The type of experimentation regarding IFN and IFN/antiviral treatment of SARS is fairly routine. However, post-filing literature suggests that neither IFN nor IFN/antiviral treatments are effective in the treatment of SARS. Furthermore, experimental anti-SARS antivirals, apparently effective vaccines, clinical and veterinary testing as well as animal control measures suggest that the rare transmission of SARS-CoV that occurred in 2002-2003 and re-emerged in 2003-2004 is not likely to reoccur and which virtually precludes implementation of proposed trials in humans except in China.

Given the breadth of the claims, the lack of guidance in the specification, and the unpredictability of the art, it would require undue experimentation for one skilled in the art to use the claimed composition and method.

Response to Arguments

4. Applicant's arguments filed 7/8/2008 have been fully considered but they are not persuasive. Applicants arguments are twofold: 1) Therapeutic methods need not be ready for clinical application in order to be enabled and 2) clinical efficacy [is not] a requirement for patentability. Citing *In re: Brana*, Applicants point out that there is an expectation in the pharmaceutical arts that additional experimentation

is expected after filing of a patent application in order to perfect clinically effective methods. Applicants further argue that Interferon-beta 1A inhibition of tissue SARS-CoV replication and cytopathology of a continuous cell line (Vero).

The Examiner fully appreciates and does not dispute that enablement of proposed therapeutic methods does not depend on "clinical readiness". However, in absence of clinical, animal, or cell culture data at the time of filing and/or provided by Applicant, enablement depends on the preponderance of evidence available at the time of and subsequent to filing. As demonstrated above, there is controversy in the art with respect to the role of IFNs in treatment of individuals with SARS for the following reasons: Theoretically, the role of interferon in the pathology of SARS-CoV is not well defined and it is uncertain whether exogenous IFN would exacerbate an otherwise controllable infection--studies with PBMCs obtained from uninfected donors demonstrate that there is no initial block to IFN induced proteins by SARS-CoV which supports the hypothesis that "[d]estruction of lung tissue is though to result from an **over-exuberant** immune response" and that "proinflammatory cytokines may be associated with lung infiltration and proliferation of [PBMCs]" (see, Castilletti, et al.2005 especially background and discussion sections).; clinically, the efficacy of IFN in humans infected with SARS-CoV is not well understood and several SARS experts teach away from the use of IFN in treatment of SARS; in cell culture experiments, the efficacy of antivirals depend on the cell type used in the experimental protocol with Ribavirin having very weak antiviral effects in monotherapy in Vero cells

(see, for example, Morgenstern)--indeed Ksiazek, et al. were surprised that the virus grew in Vero cells in their pioneering isolation studies because most other coronaviruses require very specific cell lines and/or infection in animals for propogation of high titer virus (see Results section). Thus, the preponderance of available evidence as well as SARS experts teach away from IFN therapy in humans; because the art teaches away from the use of IFN in anti-SARS-CoV chemotherapy and Applicant has not presented secondary evidence demonstrating a reasonable expectation of efficacy of their proposed method, the method as claimed is not enabled and the claims are properly rejected under 35 USC 112.

Conclusion

5. No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STUART W. SNYDER whose telephone number is (571)272-9945. The examiner can normally be reached on 9:00 AM-5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mary E Mosher/
Primary Examiner, Art Unit 1648

Stuart W Snyder
Examiner
Art Unit 1648

sws